UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/027,603	12/19/2001	Napoleone Ferrara	GENENT.1516CP1	4344

7590 06/03/2005

DENISE M. KETTELBERGER, Ph.D
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 06/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/027,603	FERRARA ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58,62,80-90 and 93-105* is/are pending in the application.

4a) Of the above claim(s) *58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62,80-90 and 94-105* is/are rejected.

7)☒ Claim(s) *93* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/19/01* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/14/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/14/05 has been entered.

2. Claims 58, 62, 80-90, and 93-105 are pending.

3. Claim 58 stands withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected invention.

4. Claims 62, 80-90, and 93-105, drawn to an antagonist of EG-VEGF wherein the antagonist is an antibody are being acted upon in this Office Action.

5. Claim 94 is objected to because "admixuture" is misspelled.

6. Claims 85 and 100 are objected to because "hybridoma cells" should have been "hybridoma" since "cells" is redundant.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 62, 80-90 and 94-105 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an antagonist of EG-VEGF wherein the antagonist is an antibody or antibody fragment that specifically binds a polypeptide consisting of amino acid residues 20-105 of SEQ ID NO: 2, (2) an antagonist of EG-VEGF wherein the antagonist is an antibody or antibody fragment that specifically binds a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, (3) An antagonist of EG-VEGF wherein the antagonist is a monoclonal antibody or binding fragment thereof wherein the monoclonal

antibody is produced from hybridoma cells having ATCC accession number PTA-4119, PTA-4120, PTA-4121 or PTA-4122, (4) the antibody or antibody fragment mentioned above wherein the antibody or antibody fragment is a humanized antibody, or humanized antibody fragment, a Fab, Fab', F(ab)'2 or Fv fragment, (5) A composition comprising said antibody or antibody fragment mentioned above and a pharmaceutically acceptable carrier, and (6) A kit or article of manufacture comprising a container; a label on the container, and the composition comprising the antibody or antibody fragment that specifically binds to EG-VEGF comprising an amino acid sequence of SEQ ID NO: 2, or a monoclonal antibody produced from hybridoma cells having ATCC accession number PTA-4119, PTA-4120, PTA-4121 or PTA-4122, **does not** reasonably provide enablement for (1) any and all "antagonist" of EG-VEGF that inhibits proliferation of adrenal cortex endothelial cells induced by a polypeptide "comprising" amino acid residues 20-105 of SEQ ID NO: 2, (2) any and all antagonist of EG-VEGF, wherein the antagonist comprises an antibody or antibody fragment that specifically binds a polypeptide "comprising" amino acid residues 20-105 of SEQ ID NO: 2, (3) any and all antagonist of EG-VEGF, wherein the antagonist comprises an antibody or antibody fragment that specifically binds a polypeptide "comprising" amino acid residues 20-105 of SEQ ID NO: 2 wherein the antibody or antibody fragment is any monoclonal antibody or monoclonal antibody fragment, any chimeric antibody or chimeric antibody fragment, any humanized antibody or humanized antibody fragment, any antibody fragment is Fab, Fab', F(ab')2 or Fv fragment, (4) any and all antagonist of EG-VEGF, wherein the antagonist is any "monoclonal antibody fragment" produced from hybridoma cells having ATCC accession number PTA-4119, PTA-4120, PTA-4121 or PTA-4122, (5) any composition comprising any antagonist of EG-VEGF, wherein the antagonist comprises an antibody or antibody fragment that specifically binds a polypeptide "comprising" amino acid residues 20-105 of SEQ ID NO: 2 in a admixture with a carrier or a pharmaceutically acceptable carrier, and (6) any antibody or antibody fragment that competes with a monoclonal antibody produced from hybridoma cells having ATCC accession number PTA-4119, PTA-4120, PTA-4121 or PTA-4122 for binding to a polypeptide "comprising" amino acid residues 20-105 of SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8

USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only four monoclonal antibodies 1C6, 2A3, 2A8 and 4H9 produced by hybridoma having the accession number PTA-4119, PTA-4120, PTA-4121 or PTA-4122, respectively, that bind specifically to human EG-VEGF comprising SEQ ID NO: 2 as shown in Figure 21 for diagnostic assays. The specification discloses only two monoclonal antibodies 1C6 and 4H9 have neutralizing activity using a cell-based proliferation assays (See Figure 21, see error bar). The specification discloses the EG-VEGF or VEGF antagonist may, for example be an anti-EG-VEGF or anti-VEGF antibody, respectively, specifically including antibody fragment. In another embodiment the EG-VEGF or VEGF antagonist is a small molecule (page 7).

The specification does not teach how to make and use any antagonist of EG-VEGF mentioned above because there is insufficient guidance as to the structure of the antagonist without the amino acid sequence of the antagonist (claim 62) since the EG-VEGF antagonist may be a small molecule. Further, the term "comprising" is open-ended. It expands the polypeptide of SEQ ID NO: 2 to include additional amino acids at either or both ends. There is a lack of guidance as to which amino acids to be added to amino acid residues 20-105 of SEQ ID NO: 2, let alone the EG-VEGF antagonist inhibits proliferation of adrenal cortex-derived endothelial cells.

Stryer *et al,* of record, teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages). Given the unlimited number of antagonist to EG-VEGF, it is unpredictable which undisclosed antagonist inhibits the proliferation of adrenal cortex-derived endothelial cells induced by any EG-VEGF polypeptide.

With regard to claim 80, again, the term "comprising" is open-ended. It expands the polypeptide of SEQ ID NO: 2 to include additional amino acids at either or both ends. There is insufficient guidance as to the binding specificity of the claimed antibody or antibody fragment.

Kuby *et al*, of record, teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide.

Abaza *et al,* of record, teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular). Since the polypeptide and the binding specificity of the antibody in claim 80 are not enabled, it follows that any monoclonal antibody, chimeric antibody, humanized antibody and fragment thereof are not enabled.

With regard to claims 85 and 100, it is known that only monoclonal antibody is produced by hybridoma. However, antibody fragment is produced by protease cleavage of the monoclonal antibody, not by hybridoma as claimed.

Harlow *et al*, of record, teach antibody fragment such as Fab or F(ab')2 fragments are produced by papain and pepsin, respectively (see Figure on page 627, in particular). The specification does not teach any monoclonal antibody fragment is produced from hybridoma cells having ATCC accession number PTA-4119, PTA-4120, PTA-4121 or PTA-4122.

With regard to antagonist of EG-VEGF "comprises" any antibody or antibody fragment that specifically binds to a polypeptide "comprising" amino acids residues 20-105 of SEQ ID NO: 2, the term "comprises" is open-ended. It expands the antagonist to include additional polypeptides at either or both ends of antibody or antibody fragment that specifically binds a polypeptide comprising amino acid residues 20-105 of SEQ ID NO: 2 to read on a fusion protein (claim 80). Further, the term "comprising" is open-ended. It expands the polypeptide fragment to which the antibody binds to include additional amino acids at either or both ends of the polypeptide. There is insufficient guidance as to the binding specificity of the claimed antagonist antibody. Without he amino acid sequence of all EG-VEGF to which the claimed antibody binds, it is unpredictable which undisclosed antibody has antagonistic activity to EG-VEGF that induced proliferation of endothelial cells. Further, there is a lack of *in vivo* working example demonstrating *any* composition mentioned above are effective for treating *any* disease such as diabetes, infertility, polycystic ovary syndrome, or cancer.

Fogarty *et al,* of record, teach targeting angiogenesis using VEGF antagonist is a promising anticancer approach, however, the twelve recent failures in clinical trials using VEGF antagonist, indicate the unpredictability of angiogenesis inhibitors for cancer treatment.

Without the amino acid sequence of any and all antagonist of EG-VEGF and the binding specificity of the claimed antibody, it would take undue experimentation for one skill in the art to make and use such antagonist commensurate in scope with the claimed commensurate in scope with these claims. Since the structure of the antagonist EG-VEGF polypeptides is enabled, it follows that any antibody fragment, chimeric antibody, humanized antibody, and binding fragment thereof that binds to polypeptide comprising amino acids residues 20-105 of SEQ ID NO: 2 are not enabled. It also follows that any composition and article of manufacture comprising any undisclosed antibody mentioned above are not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 3/14/05 have been fully considered but are not found persuasive.

Applicants' position is that the specification, including examples, sufficiently enables production of antagonist antibodies and antibody fragments that a polypeptide comprising amino acids 20-105 of SEQ ID NO:2. As recited in the amended claims, Example 1 describes isolation of a cDNA clone encoding such a polypeptide. Examples 2-6 disclose expression of such a polypeptide. Example 14 demonstrates the polypeptide to be an endothelial specific mitogen that acts selectively on a defined endothelial cell type. Example 20 shows that the polypeptide induced angiogenesis in endocrine tissue but had little effect in non-endocrine tissues. Example 7 describes production of antibodies that specifically bind the polypeptide. Example 21 describes immunization of mice with the polypeptide and generation of seven different monoclonal antibodies that bound the polypeptide. Greater than 50% of the hybridomas (four of the seven

hybridomas generated) produced antagonist antibodies that inhibited endothelial cell proliferation activity induced by the polypeptide (Example 21 and Figure 21).

In response, the specification does not teach any and all antagonist of EG-VEGF, much less antagonist antibody such as monoclonal, humanized, chimeric and binding fragment thereof that binds specifically to a polypeptide "comprising" amino acid residues 20-105 of SEQ ID NO: 2. Further, the claimed antagonist of EG-VEGF in claim 62 encompasses any polypeptide, DNA, antibody, antisense and organic compound that inhibit proliferation of adrenal cortex-derived endothelial cells induced by a polypeptide "comprising" amino acid residues 20-105 of SEQ ID NO: 2. As noted, the specification discloses only seven different monoclonal antibodies that bind to the polypeptide comprising SEQ ID NO: 2. However, only four antagonist antibodies inhibited endothelial cell proliferation activity induced by the polypeptide (Example 21 and Figure 21). The specification does not teach how to make and use any antagonist of EG-VEGF mentioned above because there is insufficient guidance as to the structure of the antagonist without the amino acid or nucleic acid sequence of the antagonist (claim 62). Further, the term "comprising" is open-ended. It expands the polypeptide of SEQ ID NO: 2 to include additional amino acids at either or both ends. There is a lack of guidance as to which amino acids to be added to amino acid residues 20-105 of SEQ ID NO: 2, let alone the EG-VEGF antagonist inhibits proliferation of adrenal cortex-derived endothelial cells. With regard to claims 85 and 100, it is known that only monoclonal antibody is produced by hybridoma. However, antibody fragment is produced by protease cleavage of the monoclonal antibody, not by hybridoma as claimed. The amended claims 85 and 100 now recite "monoclonal antibody fragment is produced by hybridoma cells having the deposited ATCC accession number PTA-4119, PTA-4120, PTA-4121 or PTA-4122". Applicants are invited to point out where in the specification teaches such claim limitations.

9. Claims 62, 80-90 and 94-105 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any and all "antagonist" of EG-VEGF that inhibits proliferation of adrenal cortex endothelial cells induced by a polypeptide "comprising" amino acid residues 20-105 of SEQ ID NO: 2, (2) any and all antagonist of EG-VEGF, wherein the antagonist comprises an antibody or antibody fragment that

specifically binds a polypeptide "comprising" amino acid residues 20-105 of SEQ ID NO: 2, (3) any and all antagonist of EG-VEGF, wherein the antagonist comprises an antibody or antibody fragment that specifically binds a polypeptide "comprising" amino acid residues 20-105 of SEQ ID NO: 2 wherein the antibody or antibody fragment is any monoclonal antibody or monoclonal antibody fragment, any chimeric antibody or chimeric antibody fragment, any humanized antibody or humanized antibody fragment, any antibody fragment is Fab, Fab', F(ab')2 or Fv fragment, (4) any and all antagonist of EG-VEGF, wherein the antagonist any monoclonal antibody fragment produced from hybridoma cells having ATCC accession number PTA-4119, PTA-4120, PTA-4121 or PTA-4122, (5) any composition comprising any antagonist of EG-VEGF, wherein the antagonist comprises an antibody or antibody fragment that specifically binds a polypeptide "comprising" amino acid residues 20-105 of SEQ ID NO: 2 in a admixture with a carrier or a pharmaceutically acceptable carrier, and (6) any antibody or antibody fragment that competes with a monoclonal antibody produced from hybridoma cells having ATCC accession number PTA-4119, PTA-4120, PTA-4121 or PTA-4122 for binding to a polypeptide "comprising" amino acid residues 20-105 of SEQ ID NO: 2.

The specification discloses only four monoclonal antibodies 1C6, 2A3, 2A8 and 4H9 produced by hybridoma having the accession number PTA-4119, PTA-4120, PTA-4121 or PTA-4122 that bind specifically to human EG-VEGF comprising SEQ ID NO: 2 as shown in Figure 21 for diagnostic assays. The specification discloses only two monoclonal antibodies 1C6 and 4H9 have neutralizing activity in cell-based proliferation assays (See Figure 21, see error bar). The specification discloses the EG-VEGF or VEGF antagonist may, for example be an anti-EG-VEGF or anti-VEGF antibody, respectively, specifically including antibody fragment. In another embodiment the EG-VEGF or VEGF antagonist is a "small molecule" (page 7).

With the exception of the specific antibodies mentioned above, there is inadequate written description about the structure associated with functions of any and all antagonist of EG-VEGF as set forth in claim 62 without the amino acid sequence. Further, the term "comprising" in claims 62 and 80 is open-ended. It expands the polypeptide of SEQ ID NO: 2 to include additional amino acids at either or both ends. There is a lack of a written description as to which amino acids to be included and whether the resulting EG-VEGF antagonist still inhibits EG-VEGF mediated proliferation of adrenal cortex-derived endothelial cells, let alone the EG-VEGF antagonist would bind specifically to polypeptide comprising amino acid residues of SEQ ID NO: 2. Since the EG-VEGF amino acid sequence of all antagonist of EG-VEGF and the binding

specificity of all antagonist antibody are not adequately described, it follows that any antibody fragment, chimeric antibody, humanized antibody, and binding fragment thereof, any composition and article of manufacture comprising said undisclosed antibody and antibody fragment thereof mentioned above are not adequately described.

Given the lack of a written description of *any* additional representative species of "antagonist of EG-VEGF", and antibody that binds to human EG-VEGF "comprising" amino acid residues 20-105 of SEQ ID NO: 2, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 3/14/05 have been fully considered but are not found persuasive.

Applicants' position is that the specification sufficiently describes the claimed genus of antagonist antibodies. The amended claims are directed to a genus of antagonist antibodies that bind a polypeptide comprising amino acid residues 20-105 of SEQ ID NO: 2. As discussed above, the specification describes isolation of a cDNA clone encoding the polypeptide, expression of the polypeptide, production of antibodies that specifically bind the polypeptide, stimulating proliferation of ACE cells with the polypeptide, immunization of mice with the polypeptide and generation of seven different monoclonal antibodies that each bind the polypeptide, and screening and detecting antagonist antibodies. Antibodies that inhibited the endothelial cell proliferation activity of SEQ ID NO: 2 were identified as EG-VEGF antagonist antibodies.

In response, claim 62 encompasses any antagonist of EG-VEGF, including small molecule, and antibody. The specification discloses only four monoclonal antibodies 1C6, 2A3, 2A8 and 4H9 produced by hybridoma having the accession number PTA-4119, PTA-4120, PTA-4121 or PTA-4122 that bind specifically to human EG-VEGF comprising SEQ ID NO: 2 as shown in Figure 21 for diagnostic assays. The specification discloses only two monoclonal antibodies 1C6 and 4H9 have neutralizing activity in cell-based proliferation assays (See Figure

21, see error bar). The specification discloses the EG-VEGF or VEGF antagonist may, for example be an anti-EG-VEGF or anti-VEGF antibody, respectively, specifically including antibody fragment. In another embodiment the EG-VEGF or VEGF antagonist is a "small molecule" (page 7).

With the exception of the specific antibodies mentioned above, there is inadequate written description about the structure associated with functions of any and all antagonist of EG-VEGF including small molecule as set forth in claim 62 without the amino acid sequence. Further, the term "comprising" is open-ended. It expands the polypeptide to included additional amino acids at either or both ends of amino acid residues 20-105 of SEQ ID NO: 5. There is inadequate written description about the amino acids to be added and whether the polypeptide still induces proliferation of adrenal cortex-derived cells to proliferate. With regard to claim 80, the same reasons apply. The term "comprising" is open-ended. It expands the amino acid residues 20-105 of SEQ ID NO: 2, there is a lack of a written description about the binding specificity of the claimed antagonist antibody or antibody fragment thereof.

As noted, the specification discloses only seven different monoclonal antibodies that bind to the polypeptide comprising SEQ ID NO: 2. However, only four antibodies inhibited endothelial cell proliferation activity induced by the polypeptide (Example 21 and Figure 21). Given the lack of a written description of *any* additional representative species of "antagonist of EG-VEGF", and antibody that binds to human EG-VEGF "comprising" amino acid residues "20-105" of SEQ ID NO: 2, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus.

10. Claims 62, 80-84, 88-90 and 105 is rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

"An antagonist of EG-VEGF that inhibits proliferation of adrenal cortex-derived endothelial cells induced by a polypeptide comprising amino acid residues 20-105 of SEQ ID NO: 2" in claim 62 represents a departure from the specification and the claims as originally filed. The passages pointed out by applicant in the amendment filed 3/14/05 do not provide a clear support for the said phrase.

The "antagonist of EG-VEGF, wherein the antagonist comprises an antibody or antibody fragment that specifically binds a polypeptide comprising amino acid residues 20-105 of SEQ ID NO: 2" in claim 80 represents a departure from the specification and the claims as originally filed. The passages pointed out by applicant in the amendment filed 3/14/05 do not provide a clear support for the said phrase. In fact, Page 15, lines 20-26 of the specification discloses EG-VEGF variant polypeptide, NOT antibody or antibody fragment that binds specifically to a polypeptide comprising amino acid residues 20-105 of SEQ ID NO: 2.

The "antibody or antibody fragment that *competes* with a monoclonal antibody produced by hybridoma cells having ATCC accession PTA-4119, PTA-4120, PTA-4121, or PTA –4122 for binding to a polypeptide comprising amino acid residues 20-105 of SEQ ID NO: 2" in claim 105 represents a departure from the specification and the claims as originally filed. The passages pointed out by applicant in the amendment filed 3/14/05 do not provide a clear support for the said phrase. The specification on page 4, lines 25-29 discloses the present invention provides for a method for identifying a compound that binds to EG-VEGF. This method comprises contacting a candidate compound with **EG-VEGF** and determining whether the candidate compound binds to the EG-VEGF. In one embodiment, the assay is a competitive binding assay, i.e. the ability of the candidate compound to compete with a molecule known to bind EG-VEGF is measured. It is known that the molecule known to bind EG-VEGF is not "antibody or antibody fragment that competes with a monoclonal antibody produced by hybridoma cells having ATCC accession PTA-4119, PTA-4120, PTA-4121, or PTA-4122. Further, the candidate compound could be antibody, EG-VEGF receptors, etc and does not have to be an antibody.

11. The filing date of the instant claims 62, 80-84, 86-90, 94-99 and 101-105 is deemed to be the filing date of instant application because the none of the provisional applications have support for the limitation of "An antagonist of EG-VEGF that inhibits proliferation of adrenal cortex-derived endothelial cells induced by a polypeptide *comprising* amino acid residues 20-105 of SEQ ID NO: 2" in claim 62, the "antagonist of EG-VEGF, wherein the antagonist comprises an antibody or antibody fragment that specifically binds a polypeptide comprising amino acid residues 20-105 of SEQ ID NO: 2" in claim 80 and "antibody or antibody fragment that competes with a monoclonal antibody produced by hybridoma cells having ATCC accession PTA-4119, PTA-4120, PTA-4121, or PTA –4122 for binding to a polypeptide comprising amino acid residues 20-105 of SEQ ID NO: 2" as recited in claim 105. If applicant desires priority prior to 9/7/2000,

applicant is invited to point out and provide documentary support (i.e. page and line number and sequence of EG-VEGF) for the priority of the instant claims in 60/213,637, PCT/US/00219, 60/145,698, US99/12252, and 60/096,146. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claims 62, 80-84, 86-90, 94-99 and 101-105 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 6,485,938 B1 (filed November 16, 1999; PTO 892).

The '938 patent teaches various antagoninst such as monoclonal (See col. 46, lines 52-62, in particular), humanized and chimeric antibody (See col. 48, lines 44-53, in particular) and binding fragment thereof such as F(ab')2, Fab', Fv, scFv (see col. 47, lines 22-66, in particular) that binds to the native full-length human Zven comprising SEQ ID NO: 5 that has amino acid sequence 100% identical to the claimed amino acid sequence of SEQ ID NO: 2 (See col. 54, line 67 bridging col. 55, SEQ ID NO: 5 of '938 patent, col. 51, line 13-14, in particular). The term "comprising" is open-ended. It expands the amino acid resdiues 20-105 of SEQ ID NO: 2 to include additional amino acids at either or both ends to include the reference polypeptide to which the reference antibody binds. The reference antibody and antibody fragment appear to competes with the monoclonal antibody produced from hybridoma cells having ATCC accession number PTA-4119, PTA-4120, PTA-4121 or PTA-4122 because the reference antibody binds to the same polypeptide. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). The '938 patent further teaches a kit or article of manufacture comprising the reference antibody, a container and written instructions for using the reference antibody (See col. 54, lines 36-52, in particular). The '938 patent further teaches a

compositon comprising the reference antagonist antibody such as anti-Zven2 antibody and injectable solution (See col. 57, lines 22-36, in particular). Thus, the reference teachings anticipate the claimed invention.

14. Claim 93 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

17. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
May 27, 2005

Christina Chan

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600